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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,248	09/19/2003	Lindsay Schwarz	D5806D	5577

52034 7590 06/13/2006

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,248	SCHWARZ ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-22* is/are pending in the application.

4a) Of the above claim(s) *18-20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-17, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of March 22, 2006 to the non-final action dated December 27, 2005 has been entered. The response amended claims 1 and 17, canceled claim 8, and added new claims 18-22. Applicant further elected "intravenous injection" as the species for the gene delivery route of administration. Claims 1-7, and 9-22 are pending in the application. Claims 18-20, and 22 are withdrawn by the examiner as being drawn to non-elected species of the invention.

Claims 1-7, 9-17 and 21 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 and 14-17 were previously rejected under 35 USC § 103(a) as being unpatentable over Malone et al. (J. Biol. Chem. 269(47):29903-29907, 1994), in view of Debs (US Pat No. 5,756,353; filed Jun. 7, 1995). In view of Applicants amendment of claims 1, and 17, introducing new routes of administration, the rejection is withdrawn. However, the amendments necessitate the following new grounds of rejection:

Claims 1-7, 9-12, 14-17 and 21 are newly rejected under 35 USC 103(a) as being unpatentable over, Unger et al. (US Pat No. 5,830,430; filed Feb. 21, 1995) in view of Malone et al. (J. Biol. Chem. 269(47):29903-29907, 1994), as evidenced by the as filed specification,

stating that the promoters used in the claimed invention (that include CMV) do not have a common GRE, as determined by searching the gene bank sequences (page 40, lines 11-13).

Claims 1-7, 9-12, 14-17 and 21 embrace a method of increasing the cellular expression of a gene in a biological tissue in an animal for gene therapy, comprising delivering said gene, under the control of a promoter that does not have a glucocorticoid response element (GRE), by intravenous injection, to said animal and additionally administering a pharmacologically effective dose of a glucocorticoid.

Unger et al. describe cationic lipid compounds that include liposomes, and are useful as carriers in the intracellular delivery of pharmaceuticals and bioactive agents that include genetic material (Abstract). The intracellular delivery of the therapeutic agents described by Unger et al. is referred to as transfection (column 1). The cationic lipid compounds are described as "applicable for use *in vitro* and/or *in vivo* in methods for the treatment of diseases, including genetic diseases, which involve or require the intracellular delivery of bioactive agents." (column 17). Unger et al. state that the cationic lipid formulations can be administered to a patient in a variety of forms adapted to the chosen route of administration, with intravenous administration as the preferred route for parenteral administration (columns 26 and 27, bridging). In Example 7, Unger et al. specifically describe the administration of a plasmid DNA cationic lipid complex to rats via tail vein injection (column 40). They further state: "Cationic lipid formulations can be formulated to be sufficiently stable in the vasculature such that they circulate throughout the body and provide blood pool equilibration...The bioactive agent will then be released locally in the target tissue." (column 28). For examples of genetic materials such as genes carried on expression vectors like plasmids etc., Unger et al. include DNA which encodes at least a portion of a gene, for example, cystic fibrosis transmembrane receptor (CFTR) (column 25). Hence, lung tissue is one of the targets contemplated for gene therapy by the CFTR gene.

Unger et al. do not describe the use of a glucocorticoid to increase the cellular expression of a transfected gene. Malone et al. describe the direct injection of plasmid DNA containing lac Z and luciferase marker genes under the control of the CMV promoter into the livers of rats and cats (non-human animals). They further describe that treatment with the glucocorticoid dexamethasone enhanced and prolonged transfected gene expression (Abstract). Further stating: "Enhancement of transfected gene expression *in vivo* after treatment with dexamethasone

demonstrates that pharmacologically defined polynucleotide delivery systems will be useful for analyses of the *in vivo* interactions of genes and organisms" (last paragraph, first column, p. 29907). Therefore, Malone et al. provide the motivation to include the administration of a glucocorticoid in *in vivo* gene transfer, to increase gene expression.

Regarding the claim 3 dose limitation range of glucocorticoid administered, Malone et al. state: "Dexamethasone treatment of rats consisted of daily subcutaneous injections of 1 mg/kg" (under Experimental Procedures, p. 29903), that is within the range stated in claim 3.

In reference to the limitations of solvent and delivery via injections (claims 7 and 8), Malone et al. state: "500 μg of plasmid DNA (dilute in 2-3 ml of Dulbecco's modified Eagle medium), was injected directly into the hepatic parenchyma". Further stating: " Cats were treated with daily subcutaneous injections of 0.3 mg/kg dexamethasone, with a 1 mg/kg pre-treatment dose the day prior to plasmid injection" (under Experimental Procedures, p. 29903).

The glucocorticoid described by Malone et al. is dexamethasone. Both dexamethasone and beclomethasone are species under examination in claim 2

A person of ordinary skill in the art at the time of the instant invention would have been motivated to combine the glucocorticoid mediated enhancement of gene expression described by Malone et al. with the cationic lipid mediated gene therapy method of Unger et al., to deliver genes to an animal, because the combination of the transfection methods would increase the cellular expression of a gene in the biological tissues of the animal. Thus, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of glucocorticoid inducible promoters such as CMV operably linked to a therapeutic gene for cationic lipid mediated intravenous delivery to an animal, together with a pharmacologically effective dose of a glucocorticoid, in an amount sufficient to increase the expression of said gene, to enhance the treatment of the pathophysiological state of said animal, resulting in the practice of the instantly claimed invention. The state of the art at the time of the invention had demonstrated the routine methods for expression of genes under the control of promoters such as CMV and *in vivo* transfection of said genes for gene therapy. Therefore, an artisan of skill, having combined the elements of a non-GRE promoter and a therapeutic gene, an intravenous cationic lipid mediated delivery means for transfer of said gene to an animal and concurrent, prior or post gene delivery treatment with a glucocorticoid, would have a reasonable

expectation of success in sufficiently increasing the cellular expression of said gene in the biological tissue of said animal to enhance treatment of a pathophysiological state of the animal.

Claim 13 is rejected under 35 USC 103(a) as being unpatentable over Unger et al. (US Pat No. 5,830,430; filed Feb. 21, 1995) in view of Malone et al. (J. Biol. Chem. 269(47):29903-29907, 1994), as applied to claims 1-7, 9-12, 14-17 and 21 above, and further in view of Zhou et al. (Biochimica et Biophys. Acta 1189:195-203, 2004).

While neither Malone et al. or Unger et al describe a method of cationic lipid transfection, wherein the cationic amine is poly-L-lysine, at the time of the invention by Applicant, Zhou et al. describe DNA transfection mediated by cationic liposomes containing lipopoly L-Lysine and a helper lipid, whereby the inclusion of the helper lipid enhanced cellular uptake of the DNA complexes up to six fold. (Abstract).

A person of ordinary skill in the art at the time of the instant invention would have been motivated to combine the glucocorticoid mediated enhancement of gene expression described by Malone et al. with the cationic lipid mediated gene therapy method of Unger et al., and the lipopolylysine method of Xhou et al. to deliver genes to an animal, because the combination of the transfection methods would increase the cellular expression of a gene in the biological tissues of the animal. Thus, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of glucocorticoid inducible promoters such as CMV operably linked to a therapeutic gene for cationic lipopoly L-lysine, intravenous administration mediated delivery to an animal, together with a pharmacologically effective dose of a glucocorticoid, in an amount sufficient to increase the expression of said gene, to enhance the treatment of the pathophysiological state of said animal, resulting in the practice of the instantly claimed invention. Therefore, an artisan of skill, having combined the elements of a non-GRE promoter and a therapeutic gene, intravenous delivery for transfer of said gene to an animal and concurrent, prior or post gene delivery treatment with a glucocorticoid, would have a reasonable expectation of success in sufficiently increasing the cellular expression of said gene in the biological tissue of said animal to enhance treatment of a pathophysiological state of the animal.

Response To Claim Rejections - 35 USC § 103

Applicants arguments as they apply to the new rejections of record have been fully considered, but have not been found persuasive in overcoming the new grounds of rejection for reasons discussed in detail below.

Applicants argue that in the restriction requirement dated 10/19/05, the examiner had drawn a distinction between the different types of glucocorticoids. Further, since the glucocorticoid currently under examination is beclomethasone, and that the prior art of record teaches dexamethasone, the examiner has failed to make a *prima facie* obviousness rejection of the species under examination. While dexamethasone and beclomethasone are structurally distinct and may exert distinct physiological effects in an animal, they can still share the common feature of similarly effecting expression driven by a CMV promoter. Hence, the Office action dated December 27, 2005, indicated that the glucocorticoid species of dexamethasone has been included in the examination of the claims (under Election/Restrictions, p. 2).As such, both beclomethasone and dexamethasone were under examination. In addition, page 3 of the Office action stated that both beclomethasone and dexamethasone represent synthetic glucocorticoids that enhance the expression of genes under the control of the CMV promoter. Moreover, Applicants specification states: "These combined results of the studies of the present invention demonstrate that this effect related to glucocorticoid action on cells was a general phenomenon and was not specific to a particular glucocorticoid" (last paragraph, p. 31). Therefore, the similar effects of both beclomethasone and dexamethasone on CMV driven gene expression is admitted by Applicant.

Applicants further argue that it is evident from Malone et al. that the glucocorticoid is believed to promote enhanced expression in the tissue simply because it reduces inflammation associated with the direct injection into the tissue. Applicants additionally note that while some direct effect on gene expression is speculated by Malone et al., the reference clearly only contemplates that the effect is limited to the context of direct injection into the tissue to be treated. Applicants argument has been fully considered, but not found persuasive. Malone et al.

state: "dexamethasone treatment enhanced and prolonged transfected gene activity in this study, probably by direct transcriptional activation and possibly by reducing inflammation at the injection site." (first column, p. 29906). Therefore, Malone et al. contemplate a dual role for the effect of dexamethasone on gene expression, namely, direct transcriptional activation and the reduction of inflammation. Malone et al. additionally noted that "pCMVL transfected cells showed a greater enhancement of luciferase activity in response to dexamethasone than those transfected with pRSVL...CMV IE contains repeated sequences with glucocorticoid response element (GRE) homology." (second column, p. 29906). Thereby, teaching that dexamethasone exerts at least part of its effects on gene expression in a promoter specific fashion, and not simply by reducing inflammation at the site of gene injection. Therefore, a person of ordinary skill in the art at the time of the instant invention would be clearly taught the "dexamethasone enhancement of gene expression" (Title of Malone et al.).

Conclusion

Claims 1-7, 9-17 and 21 are not allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Claim 21 is drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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Examiner, USPTO, AU 1633

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PRIMARY EXAMINER